ALBERTA HERITAGE FOUNDATION FOR MEDICAL RESEARCH

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AHFMR Mission

AHFMR supports a community of researchers who generate knowledge that improves the health and quality of life of Albertans and people throughout the world. AHFMR's long-term commitment is to fund basic, patient and health research based on international standards of excellence and carried out by new and established investigators and researchers in training.

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research news

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Production Notes

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Risk science—in which the best justification for legal restraint on behaviour is the harm principle—has emerged as the dominant decision-making tool for these sorts of evaluations, Dr. Brunk explains. "But safety is a value judgment and the identification of risk can be a social and political process that is sometimes driven by media coverage."

In an ideal science-based scenario, Dr. Brunk says, scientists would first identify the potential harms associated with a new health technology, then assess the risk of the harm materializing, and finally make a recommendation to the regulators on whether or not to approve the technology. In the real world however, scientists often have to make a decision before all the data is available. Even when the decision is based upon reliable science, the lay public may reject the expert recommendation.

A typical response of scientific experts is to explain the latter by pronouncing that people don't understand risk and behave irrationally. "It makes no sense to a scientist that a person who skydives will also demand organic food, for example," says Dr. Brunk. "To a risk expert this type of behaviour is irrational."

But acceptable risk is defined as that which is acceptable to society or to those who bear the risk—a judgment that involves more than scientific assessment. Risk acceptability is also based on underlying political, social, and religious values. Ethical concern is one of these values. "The high level of unease around human cloning is largely due to fundamental ethical concerns," Dr. Brunk explains. "Risk generated by activities considered ethical is deemed much more acceptable."

One of the most important factors in the public's acceptance of a particular risk however, is simply the trustworthiness of the person or persons who assess and manage the risk. As an example, Dr. Brunk points to the mismanagement of information regarding the relationship between Mad Cow disease (BSE) and its human variant Creutzfeldt-Jakob disease, which most scientists believe to be caused by eating BSE-contaminated meat products. Experts initially claimed there was no link between the two diseases, a judgment subsequently undermined by new scientific evidence. "The impact of this mismanagement has dramatically affected the acceptability of genetically modified foods in the UK and Europe," he says. "The trustworthiness of the risk managers has been eroded."

Ultimately, Dr. Brunk says, the risks of medical biotechnology are much more broadly accepted than those of agriculture biotechnology for reasons that include the prospects of improved health for the persons bearing the risk, the trustworthiness of the medical profession, and the perception of rigorous government testing of the former technology.

After being consulted, people often feel that their participation didn't influence the final decisions that were made.

The public stake in health policy

In a democracy, most people want—and are entitled to—some say in looking after their health. "It's increasingly a concern of the public to be involved in the direction of the policies that the health sector takes," says Heritage-funded researcher Dr. Wilfreda Thurston.

Dr. Thurston is leading a joint team from the University of Calgary and the Calgary Health Region (CHR), investigating how to best develop and implement at the regional level effective public participation in health policy. "We want to look at mechanisms for enhancing public participation in the Calgary Health Region," she says.

The study arose from Dr. Thurston's work in a broad-based committee that developed a public participation framework for the CHR. Released in 2001, the document outlines the values, operating principles, and opportunities for public participation–defined as "the process by which public concerns, needs, and values are incorporated into governmental decision making".

Scientific literature indicates that effective public participation provides decision-makers with more informed policy that reflects the community's values and responds to its needs, Dr. Thurston notes. However, for a host of reasons, even well-intentioned initiatives can sometimes go awry. After being consulted, people often feel that their participation didn't influence the final decisions that were made.

Dr. Thurston says that sometimes people aren't clear on who is making the decision and on the many factors involved. This is especially true in a large and complex organization like the CHR, where policy decisions are made on multiple levels and, ultimately, by the provincial government. "It's usually not a simple cause-and-effect relationship between a public's input and what happens," she notes.

Occasionally, public participation is sought even though a policy decision has already been reached. "If you don't really need the information and you don't plan to use it, it's better to use public relations to educate people about why the decision was made," Dr. Thurston says.

Another thorny issue is defining who "the public" is. Dr. Thurston points out that, in reality, there are various publics–from healthcare providers to formal advisory committees to single-interest advocacy groups. It is important for all parties to understand and acknowledge that the consultation process "is one of negotiating power and influence," she says.

The research partners in this study are focusing on evaluating and improving public participation processes related to aboriginal health, children's health, women's health, and ethno-cultural communities. The research includes doing face-to-face interviews, conducting focus groups, attending meetings, and reviewing documents with long-standing organizations like the region's Aboriginal Health Council, the Family Liaison Council at the Alberta Children's Hospital, and the CHR–Salvation Army partnership that, since 1996, has provided the facility and services of the Grace Women's Health Centre at the Foothills Hospital.

Research team members include Dr. Ardene Vollman, Dr. Myron Weber, Dr. Ann Casebeer, and Dr. Gail MacKean from the University of Calgary, and Bretta Maloff and Judy Bader from the CHR.

Dr. Thurston says the initial findings underline the importance of communication throughout the consultation process–from consideration of policy to following up after it has been implemented. Results of the study, to be completed early in 2003, will be shared with all the groups, as well as with the CHR board and Alberta Health and Wellness.

Dr. Thurston is an Associate Professor in the Department of Community Health Sciences in the University of Calgary's Faculty of Medicine. *Her research project is supported by the Health Research Fund, administered by AHFMR on behalf of Alberta Health and Wellness, as well as by the Calgary Health Region.*

Selected publications

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ABOVE: DR. WILFREDA THURSTON

Waiting times

How long do cancer patients spend between their first visit to the doctor and actually being diagnosed and given appropriate treatment? Dr. Juanita Hatcher hopes to shed some light upon this question through her study of referral patterns and waiting times for patients with lung and colorectal cancer—two of the most common types of cancer.

Dr. Hatcher is using data from the Capital and David Thompson health regions to determine if there is a difference in referral and treatment patterns for these two cancers between a major centre and a smaller Regional Health Authority. Data from the Alberta Cancer Registry, a computerized database of all incidences of cancer in the province, have been combined with hospital discharge data from the Canadian Institute for Health Information (CIHI), and ambulatory care data and billing data obtained from Alberta Health and Wellness (AHW). For each visit to health services, the AHW data includes information on the date of visit, facility, physician specialty, diagnoses, and the procedures the patient underwent. The Alberta Cancer Registry data includes information on the cancer diagnosis, the date of diagnosis, and the date and type of first definitive treatment.

Dr. Hatcher points out that the pattern of care between the two types of cancer is similar. "There are preliminary symptoms, such as cough for lung cancer and abdominal pain for colorectal cancer, and these are particularly important when we are looking at the physician data." She explains that the research team is trying to identify the first visit to a doctor in which it was indicated that the patient might have lung or colorectal cancer. The team then examines what referrals and procedures the patient underwent and whether there are any redundancies in these processes.

"With a lung cancer case, for example, the patient might present with a cough and be sent for an X-ray," explains Dr. Hatcher. "If the X-ray is suspicious, they may or may not be sent for a CT scan. With the results of that, or maybe prior to that, they may be referred to a pulmonologist or a thoracic surgeon, who will then re-evaluate them and may redo some or all of the tests. If it's not appropriate to conduct surgery, the thoracic surgeon may refer the patient to a pulmonologist; then they might be referred to the Cross Cancer or one of the other cancer centres. We're trying to identify patterns, to see whether tests are being repeated, and if so, whether this is because of delays in seeing a specialist."

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Dr. Hatcher and her co-investigators, Dr. Tim Winton, Dr. Charles Butts, and Dr. Christopher de Gara, hope that the information gleaned from their study can be used to plan more efficient services for lung and colorectal cancer patients. The methodology could also be extended beyond these two regional health authorities and applied at other cancer centres in other jurisdictions.

Dr. Hatcher receives support from the Health Research Fund, administered by AHFMR on behalf of Alberta Health and Wellness. The project also receives Alberta Cancer Board Bridge and Pilot funding. Dr. Hatcher is a Research Scientist at the Alberta Cancer Board, and an Adjunct Professor in the Department of Public Health Sciences (Faculty of Medicine and Dentistry) at the University of Alberta.

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Hatcher J, Hervas M. Emigration Patterns of Cancer Cases in Alberta, Canada. *Chronic Diseases in Canada* 2001; 22(1):12-17.

RIGHT: DR. JUANITA HATCHER

"The risk of having a low-birthweight baby is greater among women over the age of 35, regardless of whether they've had children before," says Dr. Tough, Assistant Professor in the departments of Paediatrics and Community Health Sciences at the University of Calgary. "We need to give women and their families the information to make informed decisions."

Doctors define low birthweight as less than 2,500 grams (about 5 1/2 pounds). The smaller the baby, the greater the risk of such long-term problems as developmental delays, blindness, deafness, and cerebral palsy. Statistics show that Alberta has one of the highest rates of low birthweight in Canada. Yet when Dr. Tough looked at the provincial database for live births, she found that for women under age 35, Alberta's incidence of low birthweight since 1990 has averaged 5.8%—about the same as the national average. However, for women aged 35 and over, the incidence of low birth weight has risen to 7.2% since 1990.

risks

At the same time, more women in Alberta are waiting longer to become mothers. The proportion of women aged 35 and over who are having children has increased from approximately 8% in 1990 to almost 20% in the Calgary Health Region in 2000, and to 16% in the Capital Health Region.

"Based on these statistics, we can say that almost 80% of the change that we've had in the low-birth-weight rate since 1990 is attributable to delayed childbearing," says Dr. Tough. What is unclear, however, and what her research will investigate, is why more women are postponing childbearing and what knowledge they are basing their decision upon.

Head of the Decision Support Research Team at Alberta Children's Hospital, Dr. Tough says if the trend to delay childbearing continues among women aged 35 and over, additional healthcare resources may be required to care for a greater number of low-birthweight babies. More community-based services, such as early childhood education support and speech, physical, and occupational therapies, may also be necessary.

Dr. Tough's study will include a computer-assisted telephone survey of up to 1,500 randomly selected women in the Calgary and Capital health regions who have recently had a baby. Researchers will ask what factors influenced the women's decisions to have children when they did. These might include family influence and structure, career and education choices, emotional and physical health, income—and of course, finding the right partner, Dr. Tough says. The study will also ask the women about their understanding of the risks associated with having children at various maternal ages.

A second phase of the study will survey a similar-sized group of women to determine their reasons for deciding not to have children at this time.

Dr. Tough and her research team will partner with the United Way Calgary Children's Initiative to disseminate the results of the 18-month study to women, the community, physicians, and other healthcare providers.

Dr. Tough is a Heritage Population Health Investigator who receives additional funding from the Calgary Health Region and the Calgary Children's Initiative.

Selected publications

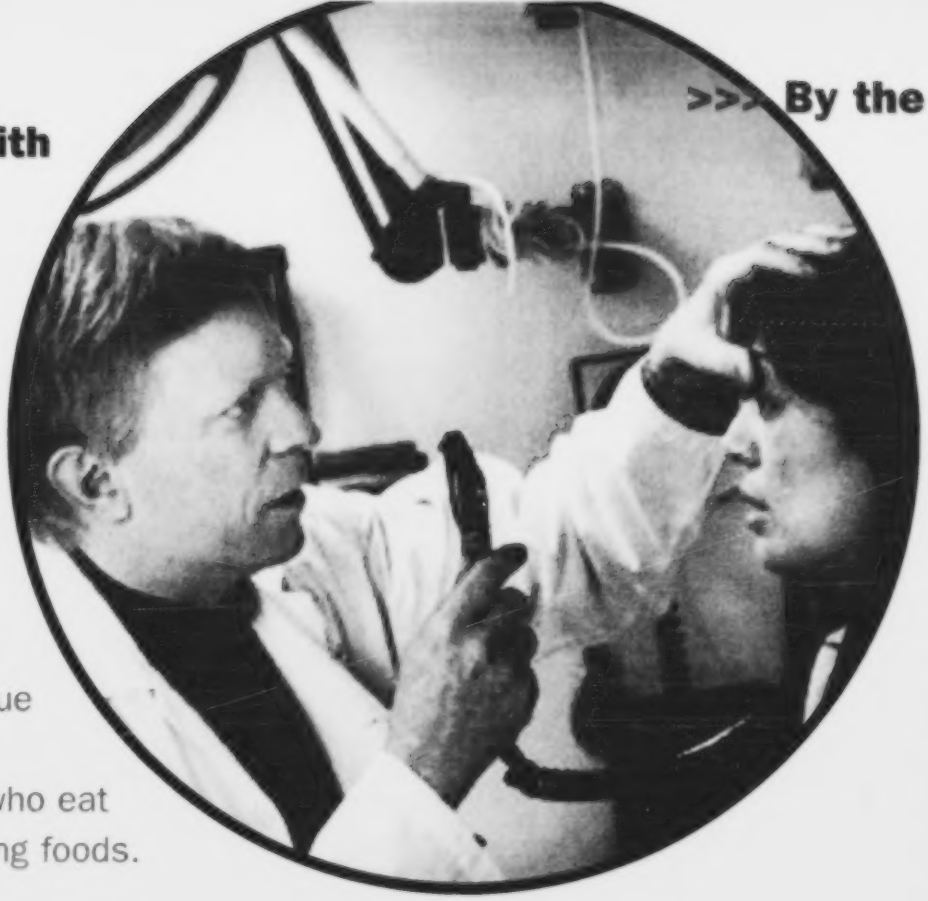
Tough SC, Newburn-Cook C, Johnston DW, Svenson LW, Rose S, Belik J. Delayed childbearing and its impact on population rate changes in lower birth weight, multiple birth, and preterm delivery. *Pediatrics* 2002 Mar;109(3):399-403.

Tough S, Sauve R, Johnston D, Singhal N, Pollard J, Greene C, Christianson H, Armin H. Characteristics and outcomes of low birth weight infants from in vitro fertilization and natural conceptions. *Journal of Obstetrics and Gynaecology Canada* 2001 Jun; 23(6):503-508.

Tough SC, Greene C, Svenson LW, Belik J. Effects of in vitro fertilization on low birth weight, preterm delivery, and multiple birth. *Journal of Pediatrics* 2000 May; 136(5):618-622.

What's wrong with this picture?

A slim, athletic person suffers a heart attack at a young age due to arteries clogged by cholesterol. The picture is accurate; what's wrong is our perception that high cholesterol is an issue only for overweight, inactive individuals who eat too much of the wrong foods.



>>> By the

A **different** picture of cho

"About one in 40 to 50 North Americans have an inherited lipid disorder," says Heritage Scholar Dr. Gordon Francis, a research scientist and physician who treats patients with lipid disorders. "Their high cholesterol is not due to lifestyle factors, but to their genes."

Take his patient Shirley Chow, for example. This 45-year-old Edmonton woman has battled the consequences of abnormally high cholesterol since she was a child—beginning with cholesterol deposits in her Achilles tendons when she was only 10 years old. By the time she was 30, Shirley had had a heart attack and coronary bypass surgery. In May 2002, a large cholesterol-containing tumour was removed from her brain.

"It was when I reached my twenties and started to ask questions, that I began to understand more about my condition," says Shirley. "I felt let down. I was in and out of the hospital; there didn't seem to be anything that could really help me. I didn't think I could take any more."

Shirley has hypercholesterolemia, the technical name for high cholesterol in the blood. While we all need cholesterol—a natural component of our cells—too much is bad news. High cholesterol creates deposits of plaque along artery walls that can lead to heart attack or stroke.

There are two main types of cholesterol: low-density lipoproteins (LDL) and high-density lipoproteins (HDL). Triglycerides are a third type of fatty

PHOTOS: DR. GORDON FRANCIS AND SHIRLEY CHOW

time she was 30, Shirley had had a heart attack and coronary bypass surgery.

material in the blood. LDL is considered "bad" cholesterol, while HDL is considered "good". An abnormal cholesterol profile can consist of high levels of LDL, low levels of HDL, elevated triglycerides, or all three. Even with a normal total cholesterol and triglyceride level, a low level of HDL puts you at high risk of heart attack or stroke.

When she first saw Dr. Francis, Shirley's LDL levels were about 4 times higher than normal. Like some people with a genetic lipid disorder, Shirley's cholesterol has proven very hard to control despite a regimen of strict diet, exercise, and maximum doses of cholesterol-lowering drugs. "We have been able to bring her LDL levels down slightly," notes Dr. Francis, "but they are still extremely high. We need to find other things to help Shirley and patients like her."

Enter Dr. Francis' research. His focus is on the good HDL cholesterol, which removes excess cholesterol from cells. HDL is formed by a complex pathway involving a number of proteins. "Understanding this pathway is the first step toward raising HDL for the treatment and prevention of LDL cholesterol buildup," says Dr. Francis. "The key protein necessary for HDL formation is now known, giving us an exciting new direction to design drugs that would induce cells to make more HDL."

While this work is going on, Dr. Francis is also trying to establish a program for LDL apheresis, a method similar to hemodialysis which is used to treat kidney failure. LDL apheresis filters all the LDL out of patients' blood, and is usually done once every two weeks. Shirley is one of the patients who could benefit from this treatment. "In some cases where cholesterol medications are ineffective or not tolerated, measures like LDL apheresis are necessary," says Dr. Francis.

"I'm a physician and a researcher—they're not completely separate activities. When I do research, I think about my patients, I think about Shirley. The patients are why I come in to work each day. We need better treatments, and the answers will come from research."

With the dark times behind her, Shirley has adopted a different outlook on life. She is well aware of the risks of high cholesterol, but she does not dwell on them. Instead, she has embarked on a career change, from hairstyling to social work. Only a week after being released from hospital following brain surgery, she attended her graduation ceremonies from the upgrading program at NorQuest College. Now she is enrolled in the Maskwacîs Cultural College social work program at NorQuest. "I can't focus on the bad things that could happen to me. I have to be positive. It makes a difference knowing that people like Dr. Francis are not only treating me, but they are also looking for new and better ways to help me."

Dr. Gordon Francis is an Associate Professor in the departments of Medicine and Biochemistry at the University of Alberta. A Heritage Scholar, his research is also supported by CIHR (Canadian Institutes of Health Research) and the Heart and Stroke Foundation of Alberta, NWT and Nunavut.

Recent publication

Francis GA, Annicotte J-S, Auwerx J. Liver X receptors: Xcreting Xol to combat atherosclerosis. *Trends in Molecular Medicine* 2002 Oct; 8(10):455-458.

lesterol

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While this work is going on, Dr. Francis is also trying to establish a program for LDL apheresis, a method similar to hemodialysis which is used to treat kidney failure. LDL apheresis filters all the LDL out of patients' blood, and is usually done once every two weeks. Shirley is one of the patients who could benefit from this treatment. "In some cases where cholesterol medications are ineffective or not tolerated, measures like LDL apheresis are necessary," says Dr. Francis.

"I'm a physician and a researcher—they're not completely separate activities. When I do research, I think about my patients, I think about Shirley. The patients are why I come in to work each day. We need better treatments, and the answers will come from research."

With the dark times behind her, Shirley has adopted a different outlook on life. She is well aware of the risks of high cholesterol, but she does not dwell on them. Instead, she has embarked on a career change, from hairstyling to social work. Only a week after being released from hospital following brain surgery, she attended her graduation ceremonies from the upgrading program at NorQuest College. Now she is enrolled in the Maskwacîs Cultural College social work program at NorQuest. "I can't focus on the bad things that could happen to me. I have to be positive. It makes a difference knowing that people like Dr. Francis are not only treating me, but they are also looking for new and better ways to help me."

Dr. Gordon Francis is an Associate Professor in the departments of Medicine and Biochemistry at the University of Alberta. A Heritage Scholar, his research is also supported by CIHR (Canadian Institutes of Health Research) and the Heart and Stroke Foundation of Alberta, NWT and Nunavut.

Recent publication

Francis GA, Annicotte J-S, Auwerx J. Liver X receptors: Xcreting Xol to combat atherosclerosis. *Trends in Molecular Medicine* 2002 Oct; 8(10):455-458.

lesterol

Ion channels and smooth muscle

Cows, oranges, and home-run hitters all have a place in Dr. Andrew Braun's research. They're images Dr. Braun uses to describe his investigation of the structure and function of potassium ion channels, which he considers the "masters" of cellular excitability. "Without them, you'd be toast," says the Heritage Senior Scholar. "Your heart would stop. Your nerves would stop working. That would be it."

Ion channels, made of a complex of proteins, are tiny, gated passageways through the cell's outer membrane. "Think of taking four oranges and grouping them in a little square," Dr. Braun says in describing the protein structure of potassium ion channels. "In the middle of the four oranges you would have a cavity or a channel or a pore, to accommodate the movement of ions and water molecules."

Most of the cell membrane is made of lipids, fatty molecules that act as a barrier to ions (electrically charged atoms), such as sodium, calcium, chloride, and potassium. So ion channels are the "gatekeepers" that control the movement of ions. They open and close in response to a change in the electrical charge difference that is naturally generated across the cell membrane, or in response to molecular signals from inside or outside the cell.

"It's sort of like a herd of cows in a corral," Dr. Braun says. "If the gate suddenly opens, some will run out into the pasture." In a similar fashion, ions will flow through a channel's pore when the gate opens and a higher concentration of ions exists on one side of the cell membrane than on the other. This controlled flow of ions regulates cell activity such as gene expression and metabolism in nearly all organisms, from fruit flies to worms to people. Ion channels enable our muscles to contract, our hearts to pump, and our nerve cells to communicate with each other.

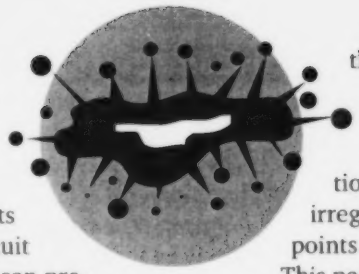
Ion channels are tiny, gated passageways through the cell's outer membrane.

Dr. Braun, a member of the University of Calgary's Smooth Muscle Research Group, is investigating how defects in potassium ion channels that regulate smooth-muscle cells cause these muscles to malfunction. Smooth (involuntary) muscle includes the muscles in our kidneys, gastrointestinal tract, and blood vessel walls; it's referred to as "smooth" because it doesn't have the pattern of lines characteristic of the aptly-named "striated" skeletal muscles–such as our biceps, triceps, and quadriceps–which are also called voluntary muscles because we have conscious control over them. Smooth muscle plays a key role in regulating blood pressure, contracting or relaxing the airways in the lungs, moving food through the gut, and passing urine from the bladder. When smooth muscle malfunctions, therefore, it can lead to problems such as hypertension, asthma, gastrointestinal disorders, and incontinence.

Ion channels are selective, meaning they allow only a specific ion to pass. Sodium-selective channels, for example, allow sodium ions to flow into the cell to trigger an "action potential"–the way that cells communicate electrically. "Every time the heart contracts, that heartbeat is generated by an action potential," Dr. Braun says.

Potassium-selective ion channels do the opposite: after the spike of electrical activity, potassium ions reduce the spike by flowing from the inside of the cell to the extra-cellular fluid outside, "effectively reversing the electrical effect produced by sodium."

Potassium ion channels, then, are crucial in returning the cell membrane to a resting state, which is required before the next pulse of electrical activity begins.



"If that movement of potassium doesn't occur correctly, or if it doesn't occur at all, then the ion channels that allow sodium and calcium to come into the cell would effectively stop," Dr. Braun says. Genetic mutations and other defects in potassium ion channels can short-circuit the cell's normal electrical activity. This can produce conditions such as irregular heartbeat, heart attack, deafness, and uncoordinated movement.

Most ion channels are controlled either by membrane voltage or by a molecular signal—called a ligand—from within or outside the cell. But Dr. Braun is trying to unravel the mystery of a unique potassium ion channel that has "dual sensors". Called a large conductance, calcium-sensitive potassium ion channel, it opens and closes in response to both voltage and the amount of calcium inside the cell. "Large conductance" simply means that it can move a huge number of ions into or out of the cell. These channels can rapidly change the voltage across the cell's membrane and alter the cell's activity—the way a home-run hitter can influence a baseball game, Dr. Braun says. This is probably why these channels have a dual-control mechanism as a built-in regulator.

Dr. Braun studies a large conductance channel that, with other potassium-selective channels, plays a starring role in regulating the amount of calcium inside smooth-muscle cells that control contraction and relaxation in blood vessels, the large airways in the lung, the gastrointestinal tract, and the bladder. Having too much calcium inside the cell could trigger too great a muscle contraction, resulting in hypertension and irregular cardiac pumping, Dr. Braun points out.

This particular ion channel is also involved in the function of the endothelium, the single layer of cells that line the blood vessels. Dr. Braun says physicians are seeing an increase in endothelium disorders, as more and more people develop type 2 diabetes. When the endothelium malfunctions, the resulting changes in blood flow can lead to cardiovascular problems and neuropathy (degeneration of nerve cells). In arteries, the endothelium produces nitric oxide, a compound which can enhance this large conductance channel and instruct the smooth muscle to dilate or relax.

Dr. Braun and his research team are trying to figure out how nitric oxide turns on a certain molecule, called cyclic GMP, that in turn switches on an enzyme that opens the large-conductance, calcium-sensitive potassium ion channels. They've developed a biochemical technique, using a radioactive tracer, to track down the exact location on the ion channel where the enzyme molecularly modifies the channel's protein structure. "If you knew how that process worked, then maybe you could design a therapeutic drug that mimicked the same thing," Dr. Braun says. Drugs that target the ion channel might influence the endothelium to control blood pressure, or expand asthmatic airway linings or alter smooth-muscle function in the gastrointestinal tract and bladder.

LEFT: DR. ANDREW BRAUN

Dr. Andrew Braun is an Associate Professor in the Department of Pharmacology and Therapeutics in the University of Calgary's Faculty of Medicine. He is an AHFMR Senior Scholar who also receives funding from the Heart and Stroke Foundation of Alberta, NWT, and Nunavut, and the Canadian Institutes of Health Research.

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Good guys and bad guys

Constant war is part of the human condition.

Each of us has an army of white blood cells, called leukocytes, that continually wage war on our behalf against foreign invaders, such as viruses, bacteria, and parasites. They also battle inflammation. Fortunately for us, these white blood cells (the "good guys") provide a great defense system. They fight hard to protect us against the "bad guys". When our immune system is strong, the good guys usually beat up on the bad guys for us and keep us well. When our immune system is impaired for any reason, we become more vulnerable and are more likely to fall ill. →

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Sometimes the body's natural defenses simply turn crazy. Instead of defending us against marauders, our white blood cells become convinced that we're the enemy and attack us with "friendly fire" instead. We can end up with an autoimmune disorder, such as rheumatoid arthritis, Crohn's disease (an inflammatory bowel condition), or asthma. Alberta researchers in the field of immunology are working painstakingly to improve our understanding of the immune system.

Trying to answer the million-dollar question

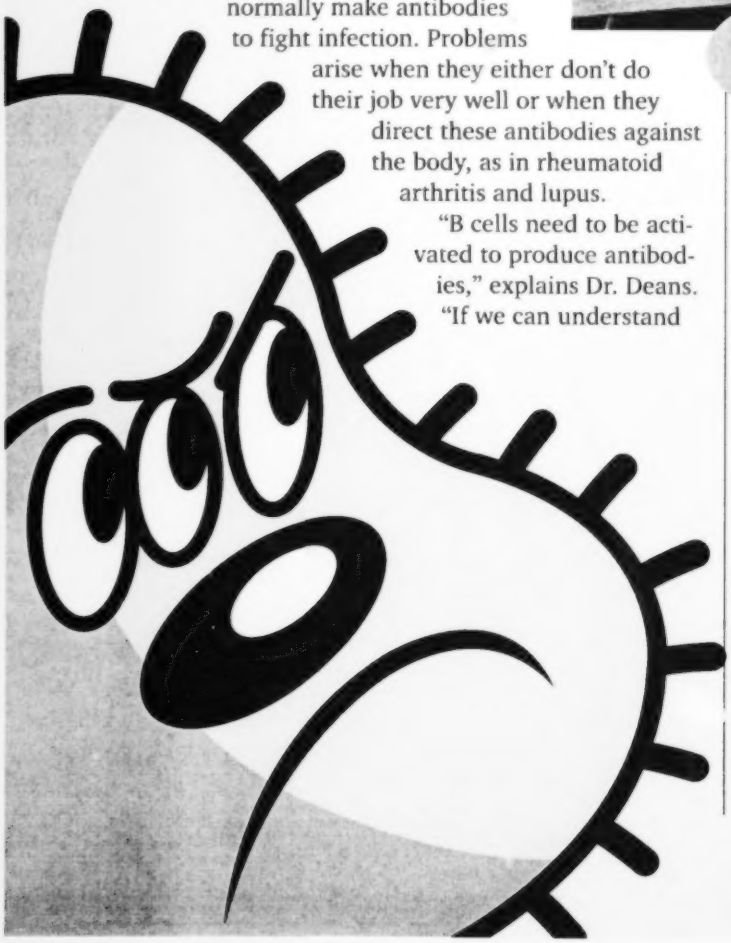
University of Calgary researcher Dr. Julie Deans is trying to answer the "huge" question of why the body's defenses sometimes attack rather than defend us. A Heritage Senior Scholar, Dr. Deans is exploring the immune system's cell signalling system and the normal controls that activate white blood cells. She and her team are currently focusing their research on B cells, a type of white blood cell. B cells normally make antibodies to fight infection. Problems arise when they either don't do their job very well or when they direct these antibodies against the body, as in rheumatoid arthritis and lupus.

B cells normally make antibodies to fight infection.

"B cells need to be activated to produce antibodies," explains Dr. Deans. "If we can understand the normal controls that regulate how they become activated, then we can possibly manipulate them to prevent autoimmunity or to treat cancer. We've made some wonderful progress. We're hitting our stride now and making some really fundamental observations that I think will turn out to be important."

Dr. Deans is investigating a specific protein, known as CD20, which is found on the surface of B cells and which is the target of an immunotherapeutic drug for B-cell cancers like non-Hodgkin's lymphoma. She and graduate student Hai-Dong Li have been able to characterize CD20 as a special type of calcium channel. Better understanding of CD20 may help scientists identify new ways to treat cancer and certain autoimmune diseases.

Dr. Deans and her team have also discovered that cholesterol plays an important role in B cells. Recently they were able to show that CD20 is in a region of the plasma membrane of B cells that is controlled by cholesterol. "This discovery has taken us into a whole new area of research," she says. "It's very exciting. We're now investigating how cholesterol regulates signalling events in the plasma membrane."



Scrambled signals: Solving the mystery of asthma

Dr. Kamala Patel, a Heritage Senior Scholar at the University of Calgary, is fascinated by the immune system. She spends hours in her lab delving into the molecular mechanisms of the immune system and

ABOVE: DR. JULIE DEANS

how they relate to inflammation and common inflammatory diseases, such as bronchial asthma.

Dr. Patel and her team have a particular interest in the movement of white blood cells. When white blood cells move from the bloodstream into infected tissue to fight invading bacteria or viruses, they cause an inflammatory response. Sometimes, too many white blood cells turn up at the wrong time and in the wrong place. Dr. Patel's research is contributing to a better basic understanding of how white blood cells get to where they are going, both when they're functioning normally and when they're not.

A cell biologist, Dr. Patel studies the proteins that act as traffic signals to direct the movement of the white blood cells in the bloodstream so they can battle invading bacteria or viruses. She also studies shear stress. "The white blood cells are normally carried along by the force of the flow of the blood through the blood vessel," she explains. "When there is an inflammatory response, the cells need to get out of the bloodstream. Imagine the forces exerted on a raft as you try to drag it out of a river and bring it to shore. This is referred to as the 'shear force' or 'shear stress'. Our lab is trying to understand how this force transmits signals that may assist in getting white blood cells up onto the bank once they have gotten to the shore's edge. In other words, how it assists them in moving into the tissue after they bind to the vessel wall."

Dr. Patel and her team are among a small number of researchers worldwide who are trying to learn more about both shear stress and a particular type of white blood cell, the eosinophil. The normal job of eosinophils is to defend the body by releasing toxins that kill parasites. Asthma, like other allergic reactions that cause an inflammatory response, triggers the production of eosinophils. They receive the signal to move into the tissue of the airways and release their toxins as if a parasite were present. In carrying out their mission, they end up damaging tissue in the lung.

When white blood cells move from the bloodstream into infected tissue they cause an inflammatory response.

Dr. Patel is attempting to figure out which signals instruct eosinophils to move from the bloodstream into the tissue. She hopes that more knowledge of the signalling process will help scientists learn how to make sure that eosinophils receive only the correct signals. The goal is to ensure that they arrive in the tissue only when they are needed, so that they don't cause damage to normal, healthy tissue. Dr. Patel and her team hope the basic research they and others working in the field are undertaking will one day help in the development of new and better drug therapies for people with asthma.

Improving asthma therapy

Dr. Harissios Vliagoftis, a Heritage Clinical Investigator at the University of Alberta, combines his love of patient care with a passion for research. A specialist in internal medicine, allergy, and immunology, he spends part of his time caring for patients with asthma at the University of Alberta Hospital in Edmonton. The remainder of the week, he's busy in his lab investigating how inflammation in the airways affects the development of asthma and triggers its symptoms. Inflammation is a two-edged sword: If the body is fighting invading bacteria, normal short-term inflammation helps the tissue heal in a few days or weeks. If too much inflammation occurs, however, we can end up with a chronic inflammatory condition, such as asthma. →

ABOVE, RIGHT: DR. MANSEL HALL LEFT: DR. HARISSIOS VLIAGOFTIS

"Asthma is a very common disease," says Dr. Vliagoftis. "We already have many good treatments for asthma. Most people with mild to moderate asthma could have their symptoms well controlled with the appropriate medical care, education, and these medications. We would like to improve asthma therapy by identifying new therapeutic targets and also by decreasing the side effects of current treatments."

Dr. Vliagoftis' current research focuses on cell-to-cell interactions in asthma. Two kinds of cells found in the lungs—the epithelial cells that line the inside of the airways and the mast cells—play an important role in these interactions. Dr. Vliagoftis is particularly interested in the role of mast cell products in airway inflammation. Mast cells release inflammatory mediators that worsen the symptoms of asthma. His goal is to interfere with this process in order to reduce the severity of disease.

Dr. Vliagoftis, a member of the Pulmonary Research Group at the University of Alberta, is collaborating with other AHFMR-funded researchers and clinicians, as well as with scientists from around the world in this field. He has already made progress with in vitro experiments in test tubes in his lab and recently started experiments using mouse models.

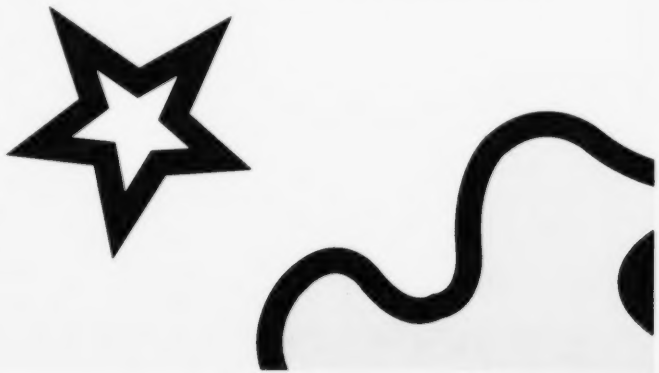
"We're getting closer to understanding exactly how the inflammation in the lungs happens in asthma," he says. "We hope to move these specific observations to clinical practice in maybe five to ten years. Better understanding of this process will also help us understand more about how current treatments work. That knowledge will help a lot in optimizing those treatments. We want to maintain how they work but reduce the side effects."

Working toward new therapies

Edmonton kidney specialist and Heritage Clinical Investigator Dr. Allan Murray is a member of the University of Alberta's organ transplant team. Part of his role as a nephrologist at the University of Alberta Hospital is to evaluate potential recipients for kidney transplants before they have surgery. When kidneys become available, he calls the recipients in and makes sure they're able to undergo the procedure. After the surgery, Dr. Murray is responsible for their immunosuppression therapy (to prevent rejection of the transplanted organ) and ensuing care.

As a dedicated physician, Dr. Murray knows only too well the impact on transplant patients of diseases and of organ rejection. As a clinician-scientist, Dr. Murray is hoping to gain a better understanding of the role of the immune system in both disease and health. He is also investigating the interaction between immune cells and the cells lining the blood vessels of a transplanted organ. Many disease states are caused when white blood cells infiltrate the tissue and function inappropriately, he explains. White blood cell recruitment is also a factor in organ rejection.

"Over the last 10 or 15 years, there has been a lot of intensive study to start to identify some of the molecule mechanisms by which white blood cells are attracted to a site of inflammation," he says. "What researchers don't understand really well, and what we're looking at, are the final phases of the recruitment of these cells from the bloodstream into the tissue. When moving from the bloodstream, they have to cross the cells (called endothelial cells) that line the walls of the blood vessels. We're investigating how the white blood cells adhere to the surface of



the endothelial cells, and how they negotiate the passage across the endothelial cells into the tissue."

Many scientists have investigated ways to interrupt the inflammatory response and develop new biological agents to combat cancer and other diseases. Clinical trials currently underway could lead to new therapeutic strategies and approaches in the next 5 to 10 years, predicts Dr. Murray.

Can ducks teach us how to fight viruses?

Edmonton biochemist Dr. Katharine Magor believes ducks can provide answers to questions about the human immune system. A Heritage Scholar, Dr. Magor is researching how viruses affect both wild and farmed ducks. Ducks are a natural host for the hepatitis virus, like the hepatitis B virus, and are also a major breeding ground for influenza viruses. Flu viruses seem capable of adapting to their host. They switch off genes in the ducks' immune system to avoid detection. Ducks experience the flu as an intestinal infection rather than a respiratory infection, as do humans. Infected ducks excrete the flu virus continually; even if they managed to clear the virus from their system, the virus remains in the pond and they become reinfected.

"My ultimate goal is to understand how viruses interfere with the duck's immune system," says Dr. Magor. "We do know that the duck's immune system is very limited. It either works or it doesn't. If we understand how the virus interferes with the duck's immune system, then we can understand how the virus shuts down our own immune defenses. We hope this leads to developing new ways to shut down the virus."

Ducks are a natural host for the hepatitis virus, and are also a major breeding ground for influenza viruses.

At the University of Alberta, Dr. Magor takes blood samples from ducks in order to get samples of their DNA for her research. The ducks used in her studies suffer no harm. She hopes her research will one day make ducks less susceptible to the flu and benefit birds as well as humans.

A vaccine for hepatitis C?

When she was a child, Dr. Babita Agrawal was terrified of needles. Now a Heritage Scholar at the University of Alberta, Dr. Agrawal has put this fear to terrific use. When still young, she began learning all about immunization and why children and sometimes adults need to have shots. As a post-graduate student, she studied tumour immunology at the University of Alberta. Then she worked for Biomira, an Edmonton biotechnology company specializing in the development of cancer vaccines and immunotherapies.

About eighteen months ago Dr. Agrawal set up a lab at the University of Alberta to undertake research into the role of the immune system in mounting effective defences against hepatitis C virus (HCV). She hopes her studies will lead to the development of a vaccine to prevent or clear HCV infection. While there are vaccines for hepatitis A and hepatitis B, there has been no progress in developing a vaccine for hepatitis C infection, which can cause significant damage to the liver and lead to long-term disability and death. Chronic HCV is a major cause of cirrhosis worldwide. Depending on the country, up to 75% of liver cancer occurs in patients with HCV infection. →

The scientific community isn't really sure how HCV affects the immune system and how it modifies the body's immune cells, explains Dr. Agrawal. "The work is really exciting, and nowhere else in the world could I be this well funded eighteen months after beginning my independent research!"

Dr. Julie Deans is an Associate Professor in the Department of Biochemistry and Molecular Biology at the University of Calgary. She is a Heritage Senior Scholar, and also receives support from the Canadian Institutes of Health Research (CIHR) and the Arthritis Society.

Dr. Kamala Patel is an Associate Professor at the University of Calgary in the departments of Physiology & Biophysics and Biochemistry & Molecular Biology. A Heritage Senior Scholar, she receives additional funding from CIHR; the Alberta Lung Association; the Canadian Breast Cancer Research Initiative (through the National Cancer Institute of Canada). Dr. Patel is also a Tier 2 chair in the Canada Research Chairs Program.

Dr. Harissios Vliagoftis is an Assistant Professor in the Division of Pulmonary Medicine at the University of Alberta. He is a Heritage Clinical Investigator, and also receives funding from CIHR and the Alberta Lung Association.

Dr. Allan Murray is an Associate Professor in the Division of Nephrology in the University of Alberta Department of Medicine. Dr. Murray is a Heritage Clinical Investigator and is also supported by CIHR; Novartis; and Aventis/Canadian Blood Services.

Dr. Katharine Magor is an Assistant Professor in the Department of Biological Sciences at the University of Alberta. In addition to her Heritage Scholarship, she receives funding from NSERC (the Natural Sciences and Engineering Research Council) and the Canada Foundation for Innovation.

Dr. Babita Agrawal is an Assistant Professor in the Department of Surgery at the University of Alberta. She is a Heritage Scholar and receives additional support from CIHR; CANVAC (Canadian Network for Vaccines and Immunotherapeutics); the Canada Foundation for Innovation; and the University Hospital Foundation.

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Singing from the same songsheet

Appropriate use of antipsychotic medications in nursing homes

Antipsychotic drugs are normally given to people with schizophrenia or various forms of psychosis. But in nursing homes, the medications are also frequently administered to patients with dementia who are considered "difficult or agitated". Some people call the medications chemical restraints, and their use is a very controversial issue.

A few years ago in the United States there was such concern over the use of these drugs in long-term care centres that legislation was enacted to establish guidelines. While no such regulatory framework exists in Canada, a pilot study done in Lethbridge three years ago suggested that the use of antipsychotic drugs might be higher than it should be, and that it varied considerably between nursing homes. This pilot study was released at a time when there was increasing interest and concern about several aspects of the use of these medications in nursing homes–such as how long a patient should be left on the medications without the prescription being reviewed.

Enter Dr. Brad Hagen and a dedicated team of nurses, physicians, and pharmacists. With a grant from the Health Research Fund, Dr. Hagen and co-investigator Dr. Paddy Quail are conducting a randomized trial evaluating an education initiative about the use of these drugs in 24 nursing homes across three southern Alberta regional health authorities: Headwaters, Chinook, and Calgary.

"We went through the literature and couldn't find any guidelines like in the United States, so we summarized what we did find and created a decision tree about when, why, and how to use these medications in nursing homes," says Dr. Hagen. The decision tree is the basis of the education campaign–a one-page document allowing healthcare professionals in all three health regions to use the same sort of guidelines to determine whether to administer the drugs. The education initiative is aimed at three groups: physicians, nursing staff, and family members. "Previous studies indicate that if you give this type of information to only one group, there is little effect, but that if you give it to both physicians and nurses, you start to see changes in everyone's clini-

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A pilot study suggested that the use of antipsychotic drugs might be higher than it should be, and that it varied considerably between nursing homes

DR. PADDY QUAIL (L) AND DR. BRAD HAGEN (R)

"The appropriate use of these drugs is our key goal."

cal practice—they start to incorporate the information. We're trying to get the whole team—nurses, physicians, and family members—all on the same songsheet."

The education portion of the study is now complete, and beginning in March, Dr. Hagen, Dr. Quail, and research project coordinator Sharon Brown will begin collecting data from pharmacy records and patient charts to determine if the use of the drugs has changed at all. Another aspect of the study is to examine the differences in use of the drugs between rural and urban nursing homes. Dr. Hagen points out that there has been a great deal of interest in the topic. "Not only are these medications potentially very expensive, driving up the cost of health care, they also have a lot of side effects and often result in patients having to go back into hospital," he explains. Side effects can include increased restlessness in patients, an increased number of falls, and various cardiac side effects.

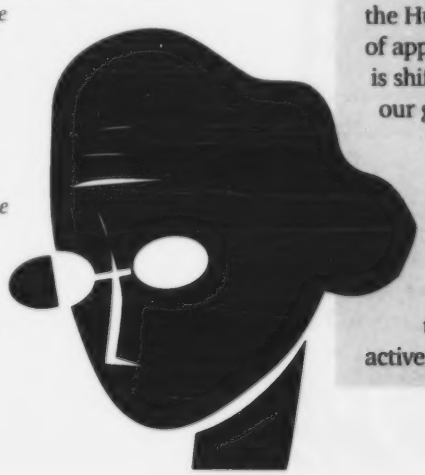
"One of the most exciting things about this study is the opportunity to collaborate between physicians and nurses, as well as between different health regions," says Dr. Quail. "We hope to educate health professionals in long-term care centres to tailor treatment to the individual. With rising drug costs and the demand for evidence-based treatments and clinical best practice, this study is expected to add to our understanding of how best to manage the needs of these unfortunate dementia patients. The appropriate use of these drugs is our key goal."

Dr. Brad Hagen is supported by the Health Research Fund, which is administered by AHFMR on behalf of Alberta Health and Wellness. He also receives funding from the University of Lethbridge Research Fund; the Alberta Gaming Research Institute; and Alberta Health and Wellness. Dr. Hagen is an Associate Professor in the University of Lethbridge School of Health Sciences.

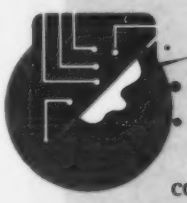
Dr. Paddy Quail, co-investigator on this Health Research Fund study, is Division Chief of Continuing Care in the Department of Family Medicine at the University of Calgary.

Selected publication

Hagen B, Armstrong-Esther C. The question of neuroleptic use in LTC. *Canadian Nursing Home* 1999 Nov/Dec; 10(4):9-17.



Ten years ago, University of Alberta chemistry professor Dr. Jed Harrison completed a landmark experiment that demonstrated the concept of a "lab-on-a-chip". He had managed to shrink some of the complex laboratory equipment needed for protein analysis to the size of a credit card. The tedious sample preparation for protein isolation and analysis could now be done in hours instead of days. "The implication was quite clear to me: this could be the beginning of a new industry," says Dr. Harrison. "I wanted it to happen in Alberta."



Now it will. Dr. Harrison is Chief Technical Officer of Advanced Integrated Microsystems (Canada) Ltd., a U of A spinoff company that is commercializing a lab-on-a-chip for protein analysis. The company is using Technology Commercialization (TC) funding from AHFMR to conduct an in-depth market analysis and develop an intellectual property strategy. With that information in place, Advanced Integrated Microsystems (AIMS) will be ready to seek the substantial investment funding it requires to move the business forward.

But back to the beginning. Despite its name, a lab-on-a-chip is not a computer chip, though it is made in a similar way. The AIMS chip is made of glass that is etched with hair-sized pathways for sample liquids. Electric fields pump the fluid and control the flow. The conventional lab procedure, with beakers and test tubes, can now be done in these tiny channels. For protein analysis—AIMS' initial target market—current preparation techniques can take one to three days; the AIMS chip can do the same job in two hours to one day.

Why is this important? With the completion of the Human Genome Project and the identification of approximately 30,000 human genes, emphasis is shifting to the proteins that are expressed by our genes. Proteins are vital to life in the cell—they provide structure, produce energy, and allow communication, movement, and reproduction. They play a key role in diseases, and can be used as targets for novel therapies or in the design of new drugs. The importance of proteins has given rise to the science of proteomics, the study of the active protein complement of an organism.

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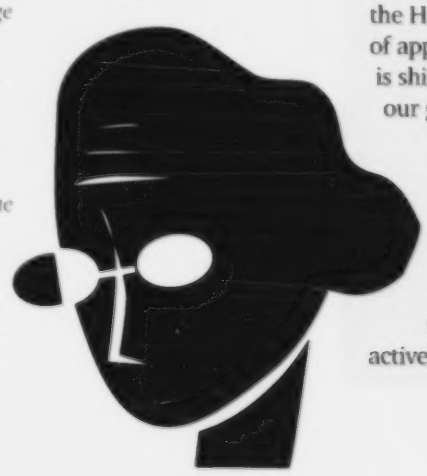
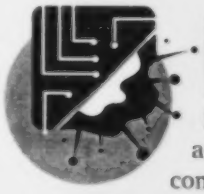
Hagen B, Armstrong-Esther C. The question of neuroleptic use in LTC. *Canadian Nursing Home* 1999 Nov/Dec; 10(4):9-17.





Now it will. Dr. Harrison is Chief Technical Officer of Advanced Integrated Microsystems (Canada) Ltd., a U of A spinoff company that is commercializing a lab-on-a-chip for protein analysis. The company is using Technology Commercialization (TC) funding from AHFMR to conduct an in-depth market analysis and develop an intellectual property strategy. With that information in place, Advanced Integrated Microsystems (AIMS) will be ready to seek the substantial investment funding it requires to move the business forward.

But back to the beginning. Despite its name, a lab-on-a-chip is not a computer chip, though it is made in a similar way. The AIMS chip is made of glass that is etched with hair-sized pathways for sample liquids. Electric fields pump the fluid and control the flow. The conventional lab procedure, with beakers and test tubes, can now be done in these tiny channels. For protein analysis—AIMS' initial target market—current preparation techniques can take one to three days; the AIMS chip can do the same job in two hours to one day.

Why is this important? With the completion of the Human Genome Project and the identification of approximately 30,000 human genes, emphasis is shifting to the proteins that are expressed by our genes. Proteins are vital to life in the cell—they provide structure, produce energy, and allow communication, movement, and reproduction. They play a key role in diseases, and can be used as targets for novel therapies or in the design of new drugs. The importance of proteins has given rise to the science of proteomics, the study of the active protein complement of an organism.

A lab on a chip

DR. JED HARRISON

As a result, protein analysis is a vital research tool in labs around the world. The traditional method involves two main steps: polyacrylamide gel electrophoresis, which separates the proteins; and mass spectrometry, which analyzes them. But there is a bottleneck between these two steps, and this is the target for AIMS' first product offering. The AIMS chip is a fully automated sample preparation microsystem for protein analysis. It takes the protein sample isolated by electrophoresis and integrates a number of procedures that must be conducted before the sample can go to a mass spectrometer.

"This is where the real innovation comes in," explains Dr. Harrison. "We've been able to develop a fully automated system for sample preparation—you put the sample in, and the 'answer' comes out. It's ready to go directly into the mass spectrometer for analysis.

"The AIMS chip not only cuts the time required for sample preparation by at least half, it also increases the throughput to the mass spectrometer. This increases the overall efficiency and reduces the cost of protein analysis."

The challenge for AIMS is to turn a working prototype into a commercial product. The company has two key industrial partners: Micralyne Inc. and MDS Sciex. Edmonton-based Micralyne is a world leader in the design and fabrication of micromachined glass, silicon, and thin-film components. It has the chip fabrication capabilities needed by AIMS. Toronto-based MDS Sciex is Canada's leading developer and exporter of mass spectrometry technology. The AIMS chip would be integrated for use with a mass spectrometer, and MDS Sciex could handle final-product assembly and sales.

"We have the critical mass to commercialize this technology," says Dr. Harrison. "Things have really come together. This is an opportunity not to be missed."

But there's one big hurdle before AIMS can go full bore. The company must find the funds for commercialization. It has already had some private investment, but will soon need major financing of about $2 million to $4 million. This is where AHFMR's Technology Commercialization program has been very helpful, says Dr. Harrison. "The TC grant has allowed us to hire consultants in marketing, manufacturing, and intellectual property. We're amassing the type of detailed business information that venture capitalists and institutional investors require before they'll invest. It would have been very difficult to do this without TC help."

Once funding is secured, AIMS' first product is scheduled to reach the market in two years. "Right now, the commercial lab-on-a-chip products are for gene analysis," notes Dr. Harrison. "AIMS is targeting applications in proteomics—a different market—and we have a considerable head start. But we still need to move quickly. I can feel the pressure."

Dr. Jed Harrison is a Professor in the Chemistry Department at the University of Alberta. In addition to Technology Commercialization funding from AHFMR, his research is supported by the Alberta Science and Research Investment Program, the Canada Foundation for Innovation, the Defense Advanced Research Projects Agency, Genome Prairie, the National Research Council, NSERC (the Natural Sciences and Engineering Research Council), and the University of Washington's Center for Process Analytical Chemistry.

Selected publication

Li J, LeRiche T, Tremblay T-L, Wang C, Bonneil E, Harrison DJ, Thibault P. Application of microfluidic devices to proteomics research: identification of trace-level protein digests and affinity capture of target peptides. *Molecular & Cellular Proteomics* 2002 Feb; 1(2):157-168.

Regulating the kidneys

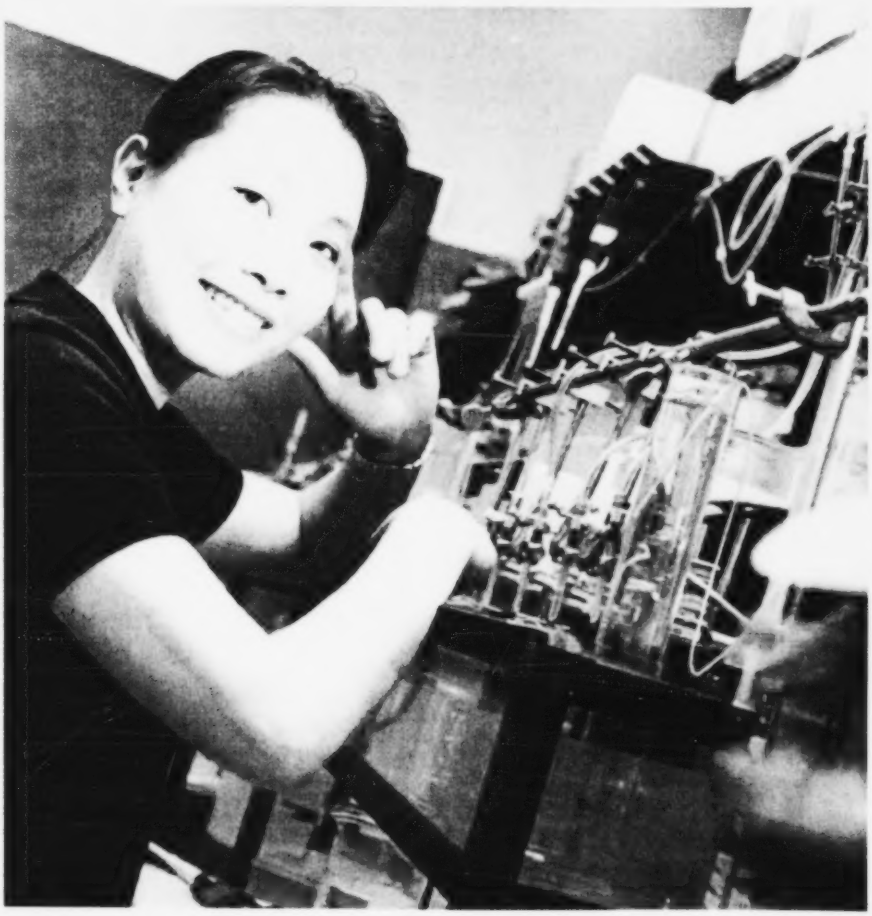
"The kidneys are key organs for our survival," says Dr. Yu Gui, who completed a Ph.D. in biochemical pharmacology in November 2002 with support from AHFMR. For her doctoral project, Dr. Gui investigated the role of a novel proteinase-activated signalling system in regulating kidney blood-vessel function.

These switches on the cell surface have been found to play a very important role in a variety of cellular functions, including blood-vessel and intestinal muscle contraction, cell proliferation, and nerve cell signalling.

A proteinase is an enzyme in the body that cuts larger pieces of protein into smaller pieces at specific locations. Certain proteinases are able to cut and activate a protein "switch" on the surface of kidney blood vessels (like cutting a fuse to activate an alarm), relaying signals to the cell interior. The activated biochemical signal cascade alters blood-vessel diameter. These switches (called proteinase-activated receptors, or PARs) on the cell surface have been found to play a very important role in a variety of cellular functions, including blood-vessel and intestinal muscle contraction, cell proliferation, and nerve cell signalling, Dr. Gui notes.

Discovered in the early 1990s, these unusual receptors are now known to also be involved in cancers, nervous system diseases, and disorders of the gastrointestinal tract. The research group Dr. Gui works with found two years ago that the receptors play a crucial role in the process whereby sensory nerves and blood-vessel cells generate pain and inflammation.

Dr. Gui used synthetic peptides (very small proteins), along with known, naturally occurring proteinases (thrombin and trypsin), to activate kidney cell receptors. Simultaneously, she measured two indicators of the kidney's performance: blood flow and blood filtration, functions that are essential for cleaning the bloodstream and excreting toxins via the urine. Both of these func-



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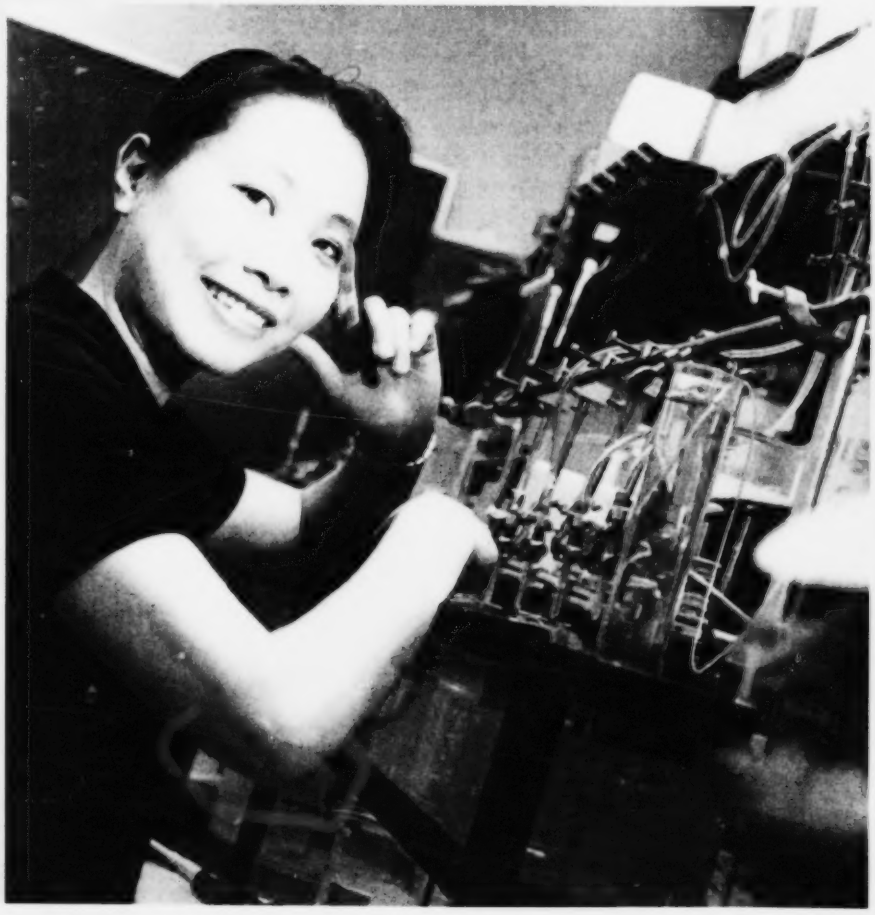

DIC occurs in the final stages of chronic kidney disease, and in acute kidney failure caused by bacterial infection or complications from pregnancy.

tions are severely impaired in patients with kidney inflammation or with a condition called DIC (disseminated intravascular coagulation). DIC occurs in the final stages of chronic kidney disease, and in acute kidney failure caused by bacterial infection or complications from pregnancy. "This disorder is very hard to manage and kills many people," says Dr. Gui.

Her research is the first to describe how two particular proteinase-activated receptors—called PAR-1 and PAR-2—regulate kidney function. Switching on PAR-1 contracts the kidney's blood vessels, reducing blood flow and filtration. Switching on PAR-2 does just the opposite, increasing both blood flow and filtration.

"Once we understand how these proteinases act on the kidney and how this action is related to kidney diseases, it should be possible to design drugs to target the proteinase-activated receptors, thereby improving kidney function," she explains. Such drugs should also be effective for diseases that involve these receptors, like inflammatory bowel disease and arthritis, which involve these receptors.

In addition to her AHFMR Studentship, Dr. Gui also received a graduate studentship from CHS/Pfizer/CIHR and a U of C graduate student fee scholarship. Dr. Gui worked as a pediatrician in her native China before coming to the University of Calgary. She received her Ph.D. in the Faculty of Medicine's Department of Pharmacology and Therapeutics.

Selected publications

Trottier G, Hollenberg M, Wang X, Gui Y, Loutzenhiser K, Loutzenhiser R. PAR-2 elicits afferent arteriolar vasodilation by NO-dependent and NO-independent actions. *American Journal of Physiology: Renal Physiology* 2002 May; 282(5):F891-F897.

Gui Y, Loutzenhiser R, Hollenberg MD. Bi-directional regulation of renal hemodynamics by activation of proteinase-activated receptors (PARs) 1 and 2 in the isolated perfused rat kidney. *American Journal of Physiology: Renal Physiology*. Submitted 2002.

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University of Calgary Department of Community Health Sciences
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Alberta Cancer Board
http://www.cancerboard.ab.ca/

The risks of delayed childbearing

Dr. Suzanne Tough's biography
http://www.calgaryhealthregion.ca/dsrt/stbio.htm

A different picture of cholesterol

Canadian Institutes of Health Research Group in Molecular and Cellular Biology of Lipids
http://cihr-mcblgroup.org

Ion channels and smooth muscle

University of Calgary Smooth Muscle Research Group
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Good guys and bad guys

The Arthritis Society of Canada
http://www.arthritis.ca

Dr. Kamala Patel's web page
http://www.ucalgary.ca/~kpatel/

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http://www.kidney.ca

American Society of Transplantation
http://www.a-s-t.org

Canada Foundation for Innovation Projects: Ducking the Flu
http://www.innovationcanada.ca/en/projects/projects_4.html

Singing from the same song sheet

Alzheimer Society of Canada
http://www.alzheimer.ca

A lab on a chip

Dr. Jed Harrison's web page
http://www.chem.ualberta.ca/faculty/harrison.htm

Regulating the kidneys

The Kidney Foundation of Canada
http://www.kidney.ca

Brett Abrahams—2002-03 Lionel E. McLeod Health Research Scholarship winner

Brett Abrahams' web page
http://www.interchg.ubc.ca/neurosci/abrahams.htm

University of British Columbia Centre for Molecular Medicine and Therapeutics
http://www.cmmt.ubc.ca/

Brett Abrahams

2002–2003 Lionel E. McLeod Health Research Scholarship Winner

How do our genes regulate our behaviour? This is one of the many questions driving the research of Brett Abrahams, a neuroscience Ph.D. student at the University of British Columbia and winner of the 2002–2003 Lionel E. McLeod Health Research Scholarship.

Brett studies the molecular mechanisms underlying brain development and behaviour. He is interested in the effects of a particular nuclear receptor (NR2E1) in the developing brain and eye, as well as its effects on aggressive behaviour. Mice lacking this gene exhibit exceptionally violent behaviour and are characterized by underdevelopment of specific regions within the forebrain and eye. A receptor that is 99% identical to this one has also been identified in humans. "Because of the striking similarity of this gene in mice and humans, we think the NR2E1 may be doing some of the same things in both species," says Brett. "I'm using a number of strategies to compare and contrast them."

Little is currently known about the biological factors underlying violence or various forms of mental illness. More knowledge of these factors could lead to better understanding of human developmental diseases associated with abnormal behaviour or brain pathology, as well as to new treatments for violent individuals. "It's clear that some genes impact behaviour," says Brett. "The challenge is to identify which ones and to understand how they interact, both with one another and with the environment."

Brett expects to complete his Ph.D. in about two years, and then find a post-doctoral position where he can continue using molecular genetics to investigate mental illness. Originally from Toronto, he hopes to be able to stay in Canada.

The Lionel E. McLeod Health Research Scholarship is given annually to an outstanding student at the University of Alberta, Calgary, or British Columbia for research related to human health. Dr. McLeod was the Head of Endocrinology at the University of Alberta, Dean of Medicine at the University of Calgary, President of AHFMR from 1981 to 1990, and President and Chief Executive Officer of the University Hospital, Vancouver.

ABOVE: BRETT ABRAHAMS

Brett Abrahams is currently pursuing a Ph.D. in neuroscience under the supervision of Dr. Elizabeth M. Simpson at the University of British Columbia's Centre for Molecular Medicine and Therapeutics. He has received numerous awards and scholarships during his academic career, including a CIHR (Canadian Institutes of Health Research) Doctoral Research Award, and the Outstanding Achievement by a Doctoral Student Award from the Children's and Women's Health Centre of British Columbia.

Selected publication

Abrahams BS, Mak GM, Berry ML, Palmquist DL, Saionz JR, Tay A, Tan YH, Brenner S, Simpson EM, Venkatesh B. Novel vertebrate genes and putative regulatory elements identified at kidney disease and NR2E1/fierce loci. *Genomics* 2002 Jul; 80(1):45-53.

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